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*Published in:*  
Nephrology Dialysis Transplantation

*DOI:*  
[10.1093/ndt/gfy187](https://doi.org/10.1093/ndt/gfy187)

*Publication date:*  
2018

*Document Version*  
Peer reviewed version

[Link to publication in Discovery Research Portal](#)

### *Citation for published version (APA):*

Rennie, T. J. W., De Souza, N., Donnan, P. T., Marwick, C. A., Davey, P., Dreischulte, T., & Bell, S. (2018). Risk of Acute Kidney Injury following community prescription of antibiotics: self-controlled case series. *Nephrology Dialysis Transplantation*, 34(11), 1910-1916. <https://doi.org/10.1093/ndt/gfy187>

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The version of record Trijntje J W Rennie, Nicosha De Souza, Peter T Donnan, Charis A Marwick, Peter Davey, Tobias Dreischulte, Samira Bell; Risk of acute kidney injury following community prescription of antibiotics: self-controlled case series, Nephrology Dialysis Transplantation, , gfy187, is available online at: <https://doi.org/10.1093/ndt/gfy187>.

# **Risk of Acute Kidney Injury following community prescription of antibiotics: self-controlled case series**

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## **Abstract**

**Introduction and aims:** Development of Acute Kidney Injury (AKI) following the use of antibiotics such as sulphonamides, trimethoprim and aminoglycosides is a frequently described phenomenon. More recently an association between fluoroquinolone use and AKI has been suggested. The aim of this study was to evaluate the risk of AKI as an unintended consequence of commonly prescribed antibiotics in a large community cohort using a method that fully adjusts for underlying patient characteristics, including potential unmeasured confounders.

**Methods:** A self-controlled case study was conducted and included all individuals aged 18 and over in the Tayside region of Scotland who had a serum creatinine measured between 1<sup>st</sup> January 2004 and 31<sup>st</sup> December 2012. AKI episodes were defined using the Kidney Disease Improving Global Outcomes (KDIGO) definition. Data on oral community prescribed antibiotics (penicillins, cephalosporins, fluoroquinolones, sulphonamides and trimethoprim, macrolides and nitrofurantoin) were collected for all individuals. Incidence rate ratios (IRR) for AKI associated with antibiotic exposure versus time periods without antibiotic exposure were calculated.

**Results:** Combined use of sulphonamides, trimethoprim and nitrofurantoin rose by 47% and incidence of community acquired AKI rose by 16% between 2008 and 2012. During the study period 12,777 individuals developed 14,900 episodes of AKI in the community, of which 68% was AKI stage 1, 16% stage 2 and 16% stage 3. The incidence rate ratio (IRR) of AKI during any antibiotic use was 1.16 95% CI (1.10 – 1.23), this was highest during sulphonamides or trimethoprim use; IRR 3.07 95% CI (2.81 – 3.35). Fluoroquinolone and nitrofurantoin use was not associated with a significantly increased rate of AKI; IRR 1.13 95% CI (0.94 – 1.35) and 1.16 95%CI (0.91 – 1.50) respectively.

**Conclusion:** Incidence of AKI rose by 16% between 2008 and 2012. In the same period use of sulphonamides, trimethoprim and nitrofurantoin increased by 47%. A significant increased

risk of AKI was seen with the use of sulphonamides and trimethoprim, but not with fluoroquinolones or nitrofurantoin.

**Keywords:** AKI, community prescribed antibiotics, self -controlled case series

## Introduction

Acute kidney injury (AKI) is associated with both short and long-term morbidity and mortality(1-4). There is increasing evidence suggesting that even a small transient rise in serum creatinine is associated with increased risk of cardiovascular disease and future development of chronic kidney disease(4-6). The National Institute for Health and Care Excellence highlighted in 2013 that AKI is increasingly common in primary care in people without any acute illness and awareness of the condition needs to be raised among primary care health professionals(7, 8).

There is emerging evidence that antibiotics commonly prescribed in the community are associated with adverse effects on renal function. In particular the development of AKI following the use of sulphonamides, nitrofurantoin and trimethoprim has been well described(9-11). A recent large British cohort study showed an increase of 72% and 48% in the odds of AKI following treatment with trimethoprim and ciprofloxacin respectively for UTI in older patients in the community(12). A large Canadian case control study also reported a two-fold increase of hospital acquired AKI during fluoroquinolone administration (17).

Potential causal effects of fluoroquinolones on collagen and connective tissue damage have been suggested following reports of tendon ruptures(13) and retinal detachment(14). Badal et al(15) described fluoroquinolone dependent iron chelation pathways causing inhibition of collagen maturation and subsequent renal toxicity. Despite plausible biological mechanisms, a potential criticism of associations from observational studies is that people who receive antibiotics are at risk of AKI for other reasons, including comorbidity, frailty and concurrent medications, which are difficult to fully adjust for.

Over four million individual antibiotic prescriptions were dispensed in the community across Scotland during 2009(16). Ten percent of these were sulphonamides and trimethoprim, 2% nitrofurantoin and 5% fluoroquinolones(17). The aim of this study was to evaluate the risk of AKI of common community prescribed antibiotics on renal function in a large community

cohort of adults, using a self-controlled case series design to avoid inter-person confounding.

## **Methods**

### ***Data sources***

The routinely recorded anonymised datasets were provided by the Health Informatics Centre (HIC) at the University of Dundee (18), which enables anonymised linkage of health records from the population of Tayside, Scotland (population approximately 400,000), using the unique identifying Community Health Index (CHI) number, which is associated with all National Health Service (NHS) healthcare use. Data from the following datasets were linked: Scottish Morbidity Record of hospital admissions (SMR01); laboratory results, medicines dispensed by community pharmacies, the Scottish Care Initiative-Diabetes Collaboration and Scottish Renal Registry.

SMR01 provides information on age, sex, postcode, admission and discharge dates. Serum creatinine measurements over the complete study period were obtained from the laboratory system. Dispensed quantity of antibiotics was available for all antibiotic prescriptions.

Missing drug name, strength or formulation values were imputed for prescriptions using those that had complete information available. The imputation was carried out in succession merging on maximum possible variables and replacing the missing values with the most common direction of use. Data were linked with the Scottish Care Initiative-Diabetes Collaboration and Scottish Renal Registry, identifying individuals with diabetes mellitus and end stage renal disease.

### ***Study population***

We identified all adult individuals, residing in the Tayside region of Scotland who had received at least one community prescribed antibiotic and had a minimum of two serum creatinine measurements between 1<sup>st</sup> January 2004 and 31<sup>st</sup> December 2012. Observation

periods for each individual were divided into those with and without exposure to an antibiotic. Individual antibiotic prescriptions with duration longer than 28 days were classed as 'chronic antibiotic use' and excluded from the analysis. Additionally, periods of antibiotic use other than via the oral route, antibiotic use during an in-patient stay or within 30 days of hospital discharge were excluded.

### ***Definitions***

Baseline serum creatinine used for the detection and classification of AKI cases was calculated as a median of serum creatinine measurements taken 8 to 365 days prior to the AKI detection date. If no such measurement was available, the nadir creatinine measurement taken between 0 to 7 days prior to the AKI detection date was used. An AKI episode was defined by the first serum creatinine measurement  $\geq 1.5$  times the baseline serum creatinine. KDIGO AKI staging criteria were used to define AKI stage(19)

A unique observation period was defined for each individual starting on the day of their first eligible antibiotic prescription or first eligible creatinine measurement during the study period (whichever was earlier) and ended on the last day of the final eligible antibiotic course, the last eligible creatinine measurement or the end of the study period (whichever was earlier). Risk periods associated with antibiotic use were defined as the start of the prescription until 14 days after the end of the prescription. Consecutive AKI episode(s) within the seven days following a previous AKI episode was considered as one AKI event. Patients who became dialysis dependent during the study period were censored from the day of starting chronic dialysis.

### ***Study design***

The self-controlled case series (SCCS) design relies on comparisons within people in a population of individuals who have both the outcome (AKI) and intermittent exposure (antibiotic use) of interest. The SCCS method is particularly useful when examining acute and recurrent outcomes after transient exposures for which exact timings are available. A



typical timeline charting AKI episodes (events) in relation to exposure to antibiotics (risk periods) is illustrated in figure 1. The major advantage of the SCCS design is that it controls for within-person confounders that do not vary significantly over time such as demographics, comorbidities and concurrent chronic medication use.

Incidence rate ratios were calculated comparing the rate of events during risk periods with the rate during all other observed time periods. Individuals were stratified by age category (18-40, 41-60, 61-80, 81 or older) and outcomes were adjusted for this single time-varying covariate. All analyses were conducted using SAS 9.4 and STATA v14.

## **Ethics**

Anonymised record linkage within the safe haven was conducted in accordance with HIC Standard Operating Procedures (SOP). These are approved by The East of Scotland Research Ethics Service and the NHS Tayside Caldicott Guardian with agreement that studies adhering to the SOP do not require individual ethical review.

## **Results**

### ***Characteristics of community antibiotic prescribing***

During the 9 year study period a total of 1,765,764 community antibiotic prescriptions were dispensed to 249,117 individuals in NHS Tayside. In line with national prescribing policies(17) the majority of individuals received penicillin (57%), 14% received sulphonamide or trimethoprim, 6% fluoroquinolones and 4% nitrofurantoin. The majority of fluoroquinolone prescribing was ciprofloxacin (91.9%). Levofloxacin was prescribed in 3.9% followed by ofloxacin (2.8%) with the remainder comprising of moxifloxacin and norfloxacin. Dosing regimens for all antibiotic exposures and for antibiotic exposures with AKI are shown in Table 1.

A 14% reduction of community prescribed antibiotic courses from 535 to 457 per 1000 population was evident between 2008 and 2012. In accordance with prescribing guidelines, reductions in fluoroquinolone, cephalosporin and macrolide prescriptions per 1000

population (-75%, -70% and -35% respectively) and increases in trimethoprim and sulphonamide (+15%) and nitrofurantoin (+163%) prescriptions per 1000 population were observed between 2008 and 2012 (Figure 2).

### ***Characteristics of individuals analysed in self-controlled case series***

Of the 249,117 individuals that received one or more antibiotic prescription between 1<sup>st</sup> January 2004 and 31<sup>st</sup> December 2012, 12,777 individuals with one or more episodes of AKI were included in our analysis. The median number of creatinine measurements over 8-365 days used to calculate the baseline for AKI was 8 (IQR: 2 -20). A flow diagram of inclusion is presented in Figure 3. Included individuals contributed to 94,859 exposed risk periods and 85,282 unexposed (control) periods during the whole study period.

The mean age of individuals at onset of first AKI was 69 (SD±18) years and 57% (7230) were female. Median creatinine was 96 µmol/L (IQR 82-117), 17% (2148) were diabetic and 70% (8952) received cardiovascular medication at the start of the observation period (Table 2).

### ***Associations between antibiotic use and AKI***

During the study period 12,777 individuals developed 14,900 episodes of AKI. Twenty one percent of individuals had two or more episodes of AKI. Sixty eight percent of episodes, were stage 1 AKI, 16% were stage 2 and 16% stage 3. Of the 2310 AKI 3 episodes, 73% were admitted to hospital with a median of 0 days to admission (IQR: 0 -16). Incidence rate of AKI was 17.6 per 100 person years in 2008 and rose to 20.5 per 100 person years in 2012. Mean number of daily doses and duration of antibiotic exposure by AKI stage is shown in Table 3. The incidence rate ratio (IRR) of AKI during antibiotic risk periods for any antibiotic as a composite endpoint compared to periods without antibiotics was 1.16 (95%CI 1.10 – 1.23). For individual antibiotic risk periods, the IRR of AKI was highest during sulphonamides or trimethoprim use; IRR 3.07 (95% CI 2.81 – 3.35). Fluoroquinolones were associated with

increased rates of AKI; IRR 1.17 (95%CI 0.98 – 1.39) () but did not reach statistical significance at the 5% level (Figure 4).

## **Discussion**

Using a self-controlled case series design, we observed a 1.16 times increased incidence rate ratio of AKI in individuals receiving community prescribed antibiotics compared to those not receiving antibiotics. This increased to a 3 fold increased risk of AKI in individuals receiving trimethoprim or sulphonamides. Duration of antibiotic exposure or number of daily doses was not associated with increased severity of AKI. Treatment with penicillin showed a reduction in IRR of 0.8 (95% CI 0.74- 0.86). According to local community antibiotic prescribing guidelines, penicillin is recommended as first choice antibiotic for non-severe chest infections, skin and ENT infections. It is likely that the low IRR of AKI represents a selected patients group in the absence of a severe systemic illness, rather than a direct effect of penicillin on renal function. In contrast to previous cohort studies (12, 20, 21), there was no increase in risk associated with oral fluoroquinolone use or antibiotics from other individual classes although there was an association of a similar order with IRR of 1.17. Fluoroquinolone induced AKI has been described in a retrospective nested case-control study from Canada (22) which reported a 2-fold increase in relative risk of hospital acquired AKI during concomitant use of fluoroquinolones. These results should be interpreted with caution due to confounding by indication and selection bias. Confounding by indication is reduced in a case-crossover design. Groups were not comparable with regards to indication for fluoroquinolone use with a greater proportion of cases suffering from genitourinary tract infections compared to the controls. Baseline characteristics also differed with significantly higher rates of hypertension, diabetes mellitus, congestive heart failure and a higher proportion of patients taking inhibitors of the renin-angiotensin system and loop diuretics in those receiving fluoroquinolones. Case reports (23-25) highlighted crystalluria induced AKI following fluoroquinolone use but this is thought to be exceedingly rare as it depends on a urine pH of greater than 6.8 to develop.

Scottish antibiotic prescribing guidance(26) published in 2010 aimed to reduce the incidence of *Clostridium difficile* infections and overall antibiotic use. This guidance promotes the use of sulphonamides, trimethoprim and nitrofurantoin amongst others for first line empirical treatment of urinary tract infections in a primary care setting. Since then, a decrease in the total community antibiotic prescriptions per 1000 population has been observed. In particular broad-spectrum antibiotics such as fluoroquinolones, cephalosporins and macrolides were prescribed on a lesser scale. This was directly associated with a 15% increase in community prescriptions of nitrofurantoin per 1000 population and a 1.6 time increase in sulphonamides and trimethoprim use per 1000 population between 2008 and 2012 in NHS Tayside. A concurrent 16% increase in incidence of AKI was observed from 2008 to 2012. This study confirmed the previously described associations between sulphonamides and trimethoprim use and AKI using data from a complete population of one Scottish Health Board over a long period of observation. Whether the increase in AKI in the community is associated with the change in antibiotic policy, as an unintended consequence, is worthy of further investigation within Tayside and across Scotland.

Our study has several strengths. Analyses were performed using routinely collected prescribing and biochemistry data from the whole NHS Tayside population (population approximately 400,000) over a 9 year period, thus comprising a heterogeneous and representative cohort with a substantial follow up period. Within-person confounding was minimised due to the use of a self-controlled case series design when comparing the risk of AKI during periods of antibiotic exposure to periods of no antibiotic use within the same patient(27).

Limitations of this study are inherently related to the retrospective design of the study and the lack of detailed information about 1) baseline co-morbidities of our cohort and 2) indication for antibiotic use. Firstly, individuals with cardiovascular disease or diabetes, accounting for 70% and 17% of our study population respectively, may have their kidney function checked more frequently in a community setting. This may have contributed to

selecting a higher risk subgroup from the Tayside population into our observed cohort. Confounding by the effect of comorbidity on AKI incidence, however, is minimised by the self-controlled case series design. Secondly, an increased incidence of AKI following sulphonamides and trimethoprim use may be related to intercurrent illnesses for which it was prescribed and it is important to note that the rise in creatinine caused by this class of antibiotics may be due to inhibition of tubular secretion rather than a “true AKI”(9, 28). Unfortunately there are no data available on the indication for antibiotic prescriptions in our cohort however current antibiotic guidance in our health board is shown in Supplementary Information. According to this guidance the majority of sulphonamides and trimethoprim, cephalosporins and nitrofurantoin prescribing were likely to be for urinary tract infections. The majority of macrolide prescribing was likely to be for chest infections as was most of the penicillin prescribing.

Using a study design which adjusted for confounding to a greater extent than other observational designs, our findings confirm the previously well-described increased risk of AKI with the use of community prescribed antibiotics, in particular sulphonamides and trimethoprim. However, we did not find any clear evidence in this large, heterogeneous cohort to suggest that fluoroquinolones are associated with increased of AKI in the community.

### **Conflicts of Interest**

TR, CM, TD, NDS, PD and SB declare no conflicts of interest. PTD reports grants from Shire Pharmaceuticals, grants from Novo Nordisk, grants from GSK, grants from AstraZeneca, grants from Gilead, outside the submitted work; and Prof Donnan is a member of New Drugs Committee of the Scottish Medicines Consortium.

### **Authors' Contributions**

SB, CM, PD, PTD and TD conceived the study, interpreted the data and drafted the article. TR interpreted the data and drafted the article. NDS analysed the data and drafted and

revised the article. All authors provided intellectual content of critical importance to the work, described and approved the final version.

### **Funding**

This study was funded by Anonymous Trust and Chief Scientist Office for Scotland.

## Figures and Tables

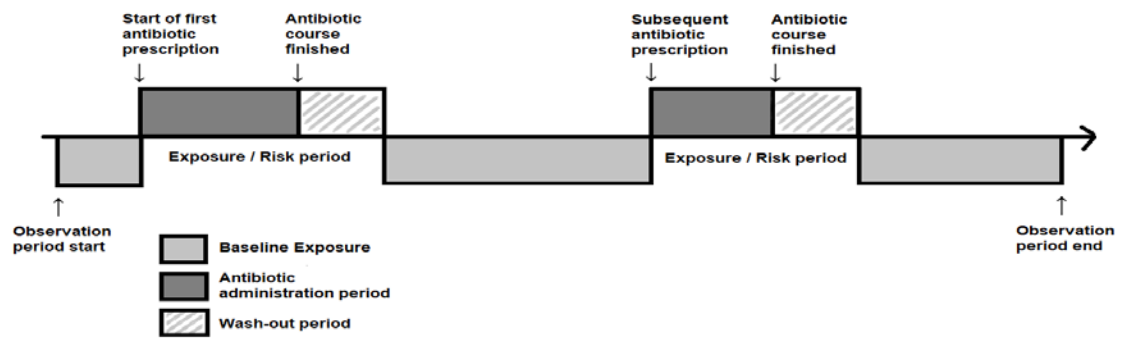


Figure 1: Self-Controlled Case Series design

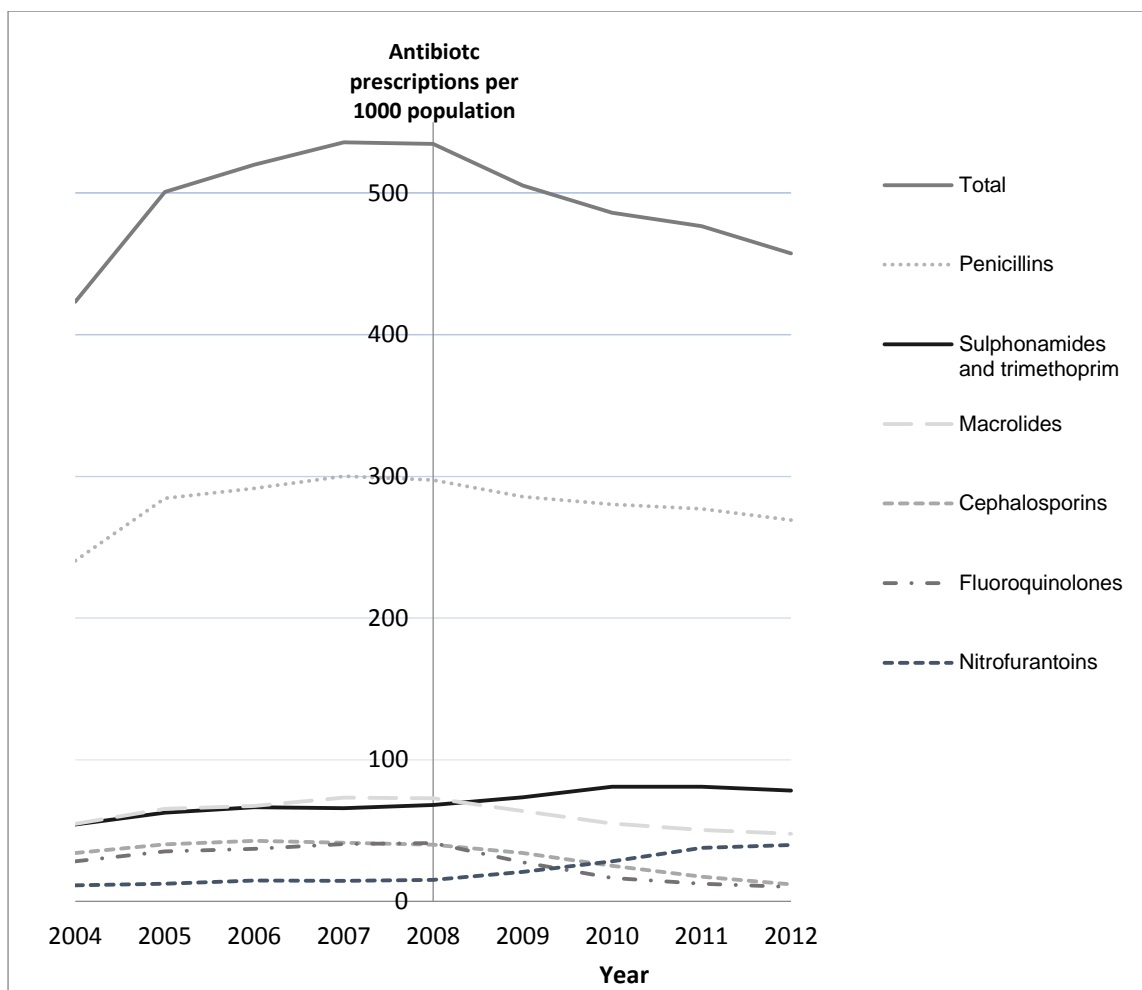


Figure 2: Antibiotic prescriptions in NHS Tayside from 2004 – 2012 per 1000 population for each of the 6 main antibiotic classes studied



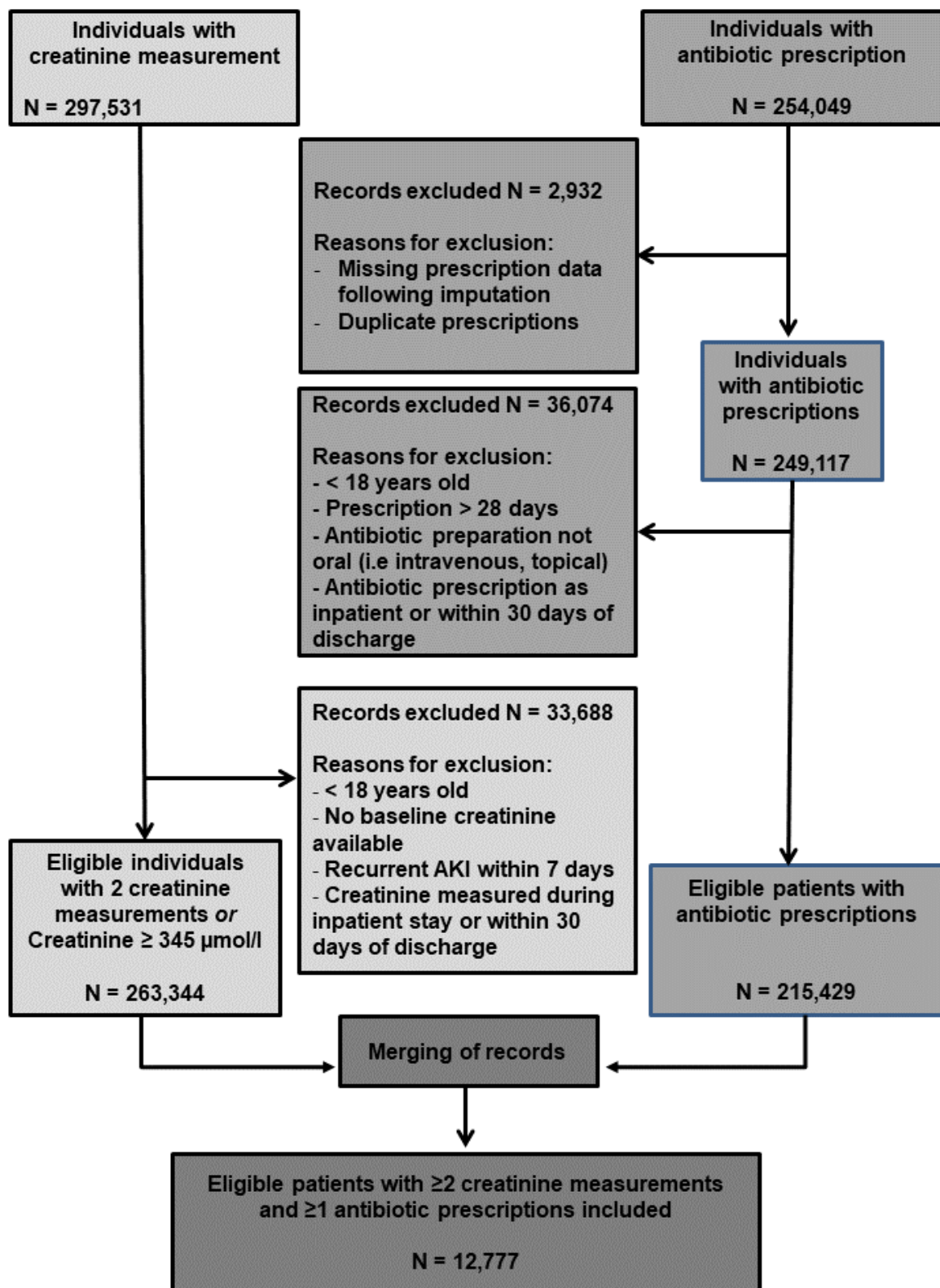


Figure 3: Flow diagram for patient inclusions

Antibiotic class	All antibiotic exposures mean (SD)		Antibiotic exposure with AKI mean (SD)	
	Number of doses per day	Duration of prescription (days)	Number of doses per day	Duration of prescription (days)
Cephalosporins	3.68 (2.44)	7.36 (3.47)	4.62 (4.19)	6.76 (1.26)
Fluoroquinolones	2.12 (1.69)	7.94 (4.65)	2.23 (2.12)	9.48 (6.79)
Macrolides	3.46 (3.27)	7.56 (3.48)	3.7 (3.54)	7.55 (3.37)
Nitrofurantoin	3.33 (3.03)	7.74 (5.66)	3.47 (4.57)	8.57 (6.68)
Penicillins	4.01 (3.83)	7.11 (2.13)	4.71 (5.06)	7.31 (2.56)
Sulphonamides & Trimethoprim	2.43 (4.15)	6.78 (5.42)	2.16 (3.23)	8.87 (7.4)

Table 1: Antibiotic dosing regimen in all antibiotic exposures and for exposures with AKI by antibiotic class

<b>N = 12777</b>	<b>Patient characteristics</b>	
	<b>Start of observation period</b>	<b>End of observation period</b>
Female; N (%)	7230 (57)	
Age; years (mean $\pm$ SD)	68.8 $\pm$ 17.6	
Receiving cardiovascular medication; N (%)*	8952 (70.1)	11058 (86.5)
Diabetes Mellitus; N (%)	2148 (16.8)	3427 (26.8)
Creatinine; $\mu$ mol/L; (median (IQR))	96 (82-117)	112 (76-174)

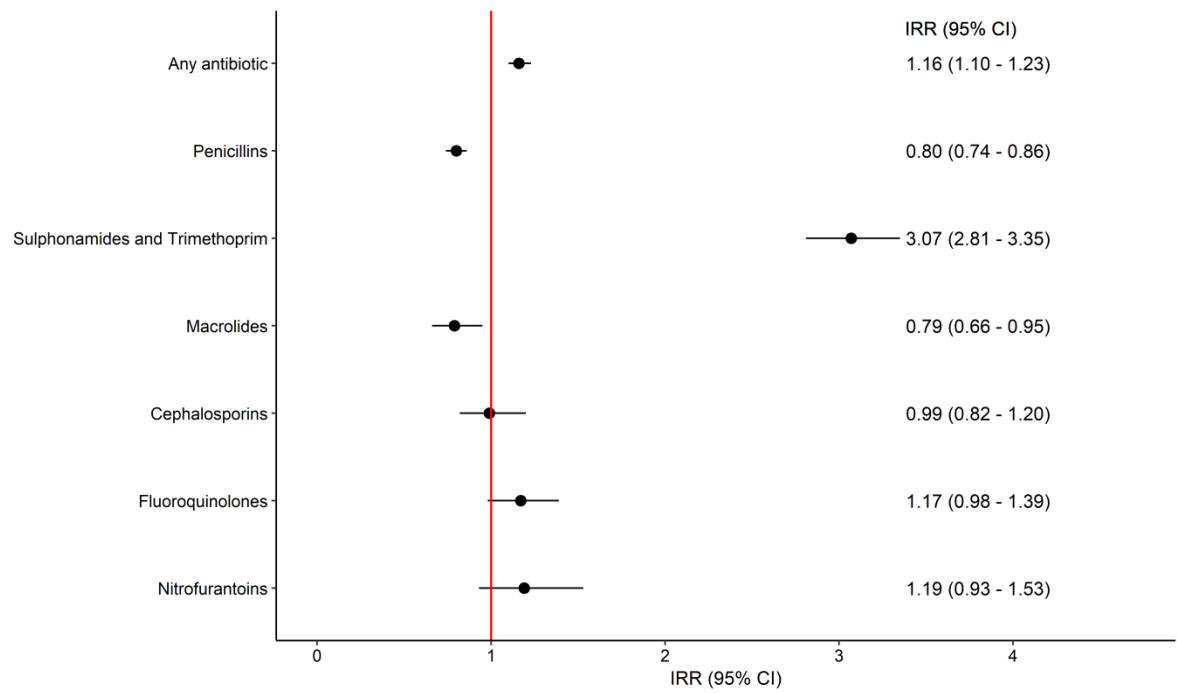
Table 2: Patient characteristics at start of observation period (N=12777)

\* Receiving cardiovascular medication is defined as any drug prescription mentioned in chapter 2 of British National Formulary, including management of arrhythmias, bleeding disorders, blood clots, blood pressure conditions, heart failure, hyperlipidaemia, myocardial ischaemia, oedema and vascular disease.

AKI Stage	Stage 1 mean (SD)		Stage 2 mean (SD)		Stage 3 mean(SD)	
Antibiotic Class	Number of doses per day	Duration of prescription (days)	Number of doses per day	Duration of prescription (days)	Number of doses per day	Duration of prescription (days)
Cephalosporins	4 (3.14)	6.81 (1.13)	5.04 (4.13)	7.23 (2.17)	6.39 (6.34)	6.38 (0.94)
Fluoroquinolones	2.32 (2.32)	7.34 (2.98)	2.05 (1.93)	14.64 (10.36)	2.19 (1.63)	8.38 (4.16)
Macrolides	3.81 (3.55)	7.43 (3.16)	2.84 (2.01)	8.63 (4.99)	4.08 (5.12)	6.92 (1.51)
Nitrofurantoin	3.61 (5.33)	8.76 (7.22)	3 (1.22)	8.67 (7.38)	3.18 (1.01)	7.5 (1.51)
Penicillins	4.34 (4.2)	7.21 (2.3)	6.49 (7.84)	7.6 (2.72)	5.09 (5.88)	7.64 (3.65)
Sulphonamides &Trimethoprim	2.03 (2.3)	8.88 (7.44)	2.7 (5.7)	9.39 (8.12)	2.71 (5.44)	7.76 (5.12)

Table 3: Mean number of daily doses and antibiotic exposure duration by AKI Stage

Figure 4: Incidence rate ratio (IRR) of AKI for antibiotic subgroup adjusted for age



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